REMARKS/ARGUMENTS

In response to the Office Action of November 14, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

In order to provide the Examiner with an opportunity to fully consider all of the issues, a Request for Continuing Examination is filed concurrently herewith.

Claim Status/Support for Amendments

Claims 1 and 36-43 are currently under examination on the merits. Claims 2-35 were cancelled in a previous Response filed on June 13, 2003. Claim 42 has been amended herein. Claims 1, 36 and 39 have been deemed allowable by the Examiner. Claims 1 and 36-43 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

In the "Background of the Invention" section a punctuation error (close parentheses) was corrected at page 1, line 21.

The disclosure of prior art, PCT/EP97/04396, at page 4 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The paragraph at page 20, beginning at line 7, was amended to correct a typographical error (moities) and to delete an extraneous word (educable). Support for this change can be found in an objective of the invention, disclosed at page 17, lines 15-18 of the instant specification.

The spotting protocol at page 21 has been amended to correct a typographical error (matrix replaced matrx).

In the "Detailed Description of the Invention" section several protocols at pages 21-25 were amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS, EPPENDORF). The titles at page 21 (line 12), page 22 (line 19) and page 24 (line 1) appeared in a bold font in the specification as originally filed. Several typographical errors within the protocols were also corrected.

In the "Detailed Description of the Invention" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 28, line 17 in order to provide explicit support for cerebrospinal fluid as recited in claim 38. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendment to claim 42 made

herein. Claim 42 was amended to provide proper antecedent basis for the term "diagnostic kit" in claim 41.

Rejections under 35 USC 112, first paragraph

Claims 37, 38 and 40-43, as presented on June 13, 2003, stand rejected under 35 USC 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time that the application was filed, had possession of the claimed invention. The Examiner indicates that this is a new matter rejection.

The Examiner asserts that claim 37 recites the limitation wherein "the sample is an unfractionated body fluid or a tissue sample" which is considered new matter.

Applicants respectfully disagree with the Examiner's assertion.

The Examiner is reminded that the subject matter need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement (see MPEP 2163.02).

As defined by the web site dictionary.com, the term "fractionate" means to divide or separate into components(see attached document as accessed from the internet; reference 1). Thus, a sample which is "unfractionated" is simply a sample which

has not been separated, i.e. fractionated into various components.

Fractionation of protein samples prior to analysis is routinely practiced in the art; reference to a sample as "fractionated" or "unfractionated" is common(see attached product brochure for ZOOM IEF Fractionator manufactured by Invitrogen, especially Figures 7b and 7c, which compare fractionated and unfractionated samples of rat liver lysate proteins shown in 2DE gels; product brochure accessed from the internet, reference 2).

Unfractionated body fluids and tissue samples are often analyzed using SELDI (surface enhanced laser desorption ionization) mass spectrometric techniques (see the instant specification at page 10, line 16 to page 11, line 9 and the attached abstract of Kuwata et al.; reference 3.

Utilization of the SELDI technique is a component of the claimed methods; clearly disclosed by the instant specification, as originally filed at page 12, lines 2-6; page 20, lines 2-6 and Figure 2, for example).

Although unfractionated body fluid and tissue samples are not described literally in the specification, the SELDI mass spectrometric technique is literally described as analyzing unfractionated body fluid and tissue samples. The SELDI mass spectrometric technique is clearly indicated to be a component of the disclosed methods.

Thus, one of skill in the art would immediately recognize that

the use of unfractionated samples in the claimed methods was contemplated by the inventors at the time that the application was filed.

Accordingly, Applicants respectfully submit that the limitation "wherein the sample is an unfractionated body fluid or tissue sample" as recited in claim 37 does not constitute new matter.

The Examiner asserts that the term "cerebrospinal fluid" as recited in claim 38 is new matter.

Applicants respectfully disagree with the Examiner's assertion.

In the "Detailed Description of the Invention" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 28, line 17 in order to provide explicit support for cerebrospinal fluid as recited in claim 38.

"CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art components(see attached document as accessed from dictionary.com; reference 4). The term "cerebrospinal fluid" and the abbreviation "CSF" are frequently used interchangeably in the art (see attached abstract of Liu et al., reference 5).

Thus, one of skill in the art would immediately recognize that the analyzing of CSF, i.e. cerebrospinal fluid, samples in the claimed methods was contemplated by the inventors at the time that the application was filed.

Accordingly, Applicants respectfully submit that the limitation "cerebrospinal fluid" as recited in claim 37 does not constitute new matter.

The Examiner asserts that the limitation "wherein said patient is a human" as recited in claim 40 is new matter.

Applicants respectfully disagree with the Examiner's assertion and contend that the limitation "wherein said patient is a human" finds support throughout the specification as originally filed.

The instant specification clearly indicates that particular significance is given to biopolymer markers associated with Syndrome X as a large segment of the adult population of industrialized countries develops this metabolic syndrome (see page 12, lines 13-17 and page 15, lines 3-8). The phrase "adult population of industrialized countries" obviously refers to human beings.

Figure 1, as originally filed, is a table disclosing specific patient information (gender, age, patient history, disease, molecular weight, protein name and sequence) for approximately 44 patients, each identified by a patient code number in column 1, who participated in the disclosed experiments. There is nothing to indicate that the patients listed in this table are anything other than human beings.

Furthermore, the Sequence Listing identifies the claimed biopolymer marker (SEQ ID NO:1) as a human peptide (organism/homo

sapiens), see, for example, the Second Substitute Sequence Listing filed on September 8, 2003. Thus, if the claimed peptide is a human peptide, one would clearly analyze human samples for the presence of such peptide.

Thus, one of skill in the art would immediately recognize that human samples were contemplated for analysis in the disclosed methods by the inventors at the time that the application was filed.

Accordingly, Applicants respectfully submit that the limitation "wherein said patient is a human" as recited in claim 40 does not constitute new matter.

The Examiner asserts that the limitation "diagnostic kit with defined composition such as SEQ ID NO:1 and antibody" as recited in claims 41-43 is new matter.

Applicants respectfully disagree with the Examiner's assertion and contend that the limitation "diagnostic kit with defined composition such as SEQ ID NO:1 and antibody" finds implicit and explicit support throughout the specification as originally filed.

Page 18, lines 5-7 of the instant specification disclose that an objective of the instant invention is to teach a diagnostic kit for determining the presence of the claimed disease specific marker (SEQ ID NO:1). Page 28, line 3 to page 33, line 2 disclose an extensive discussion of how the presence of the claimed marker is determined and what tools are used for such determination. Page 28,

lines 17-20 explicitly recites that the presence of the marker is determined using antibodies specific for the marker and detecting specific binding of the antibody to its respective marker; hence the marker and an antibody are used to determine the presence of the marker in a sample. If such marker sequence and antibodies are used in a method to determine the presence of a marker sequence in a sample, it follows that the marker sequence and antibodies would be components of a kit for accomplishing the same. Page 31, lines 9-12 explicitly recites that another objective of the invention is to provide reagents for use in diagnostic assays for the detection of the marker sequences. In the following paragraph at page 31, beginning at line 13, it is noted that the marker sequence of the invention may be used as an antigen in immunoassays for the detection of those individuals suffering from the disease evidenced by the marker sequence. Thus, the marker sequence is disclosed as a reagent in a diagnostic assay. In subsequent paragraphs (pages 31-32) it is disclosed that antibodies produced against the marker sequence are useful in immunoassays to diagnose patients with the characteristic disease linked to the marker sequence. Thus, antibodies are also described as reagents in diagnostic assays.

Accordingly, Applicants contend that one of skill in the art would immediately recognize that diagnostic kits including SEQ ID NO:1 (marker sequence) and antibodies were contemplated for use in the disclosed methods by the inventors at the time that the

application was filed.

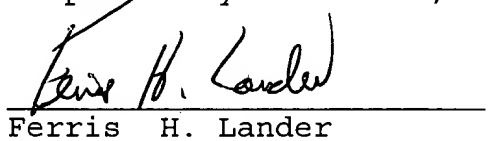
Thus, Applicants respectfully submit that the limitation "diagnostic kits with defined compositions such as SEQ ID NO:1 and antibody" as recited in claims 41-43 does not constitute new matter.

Applicants have now addressed all of the Examiner's assertions regarding "new matter" and respectfully submit, as evidenced by the above arguments, that the instant specification conveys with reasonable clarity to those skilled in the art that, as of the filing date, Applicants were in possession of the invention as now claimed (see MPEP 2163.02). Thus, Applicants respectfully request that this rejection of claims 37, 38 and 40-43 under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendment to the claim 42, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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frac·tion·ate sh t□FPRIVATE "TYPE=PICT;ALT=")
tr.v. **frac·tion·at·ed, frac·tion·at·ing, frac·tion·ates**

To divide or separate into parts; break up: "In the post-Watergate era, power has been fractionated on Capitol Hill" (Evan Thomas).

To separate (a chemical compound) into components, as by distillation or crystallization

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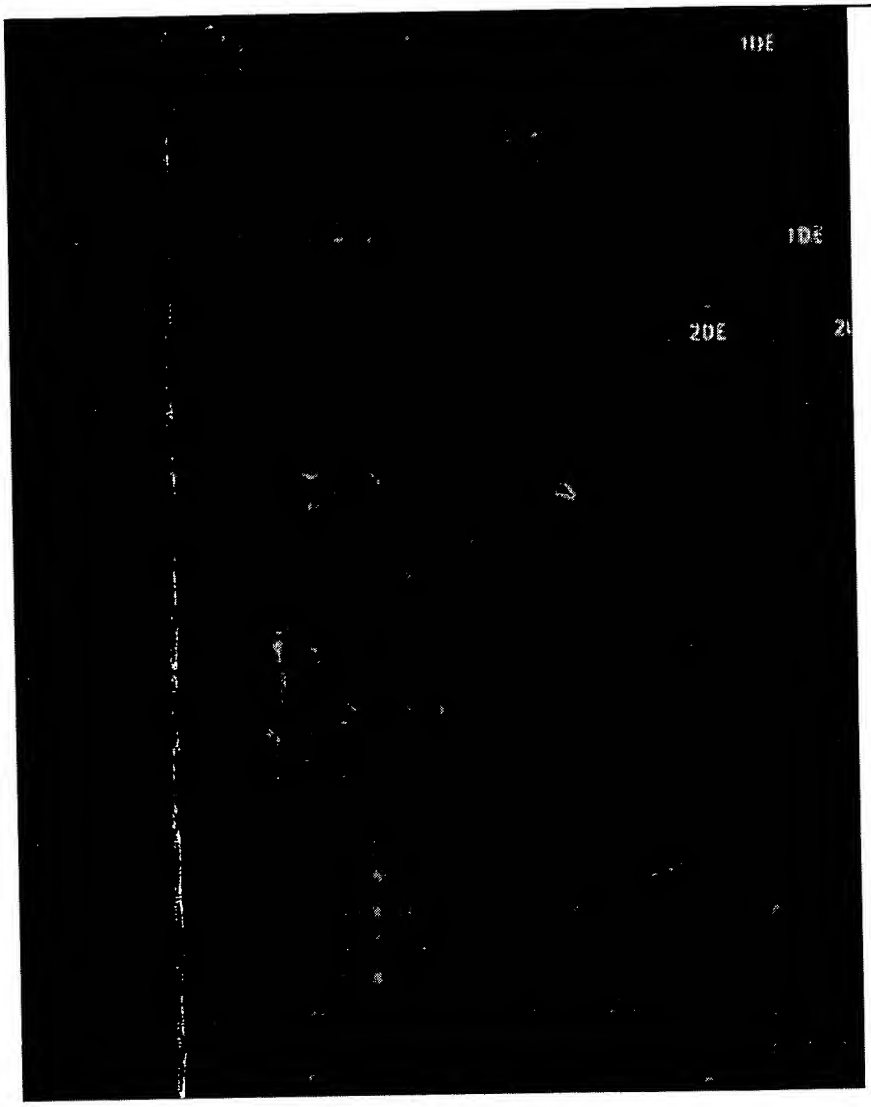
Enhance your protein profile



ZOOM® IEF Fractionator speeds and simplifies biomarker discovery

- **Solution phase IEF**–Allows easier detection of low abundance proteins and increases dynamic range of detection
- **Streamlines sample preparation**–Simple set up with all components ready to use
- **Provides superior results**–Reproducible separations over a broad pH range

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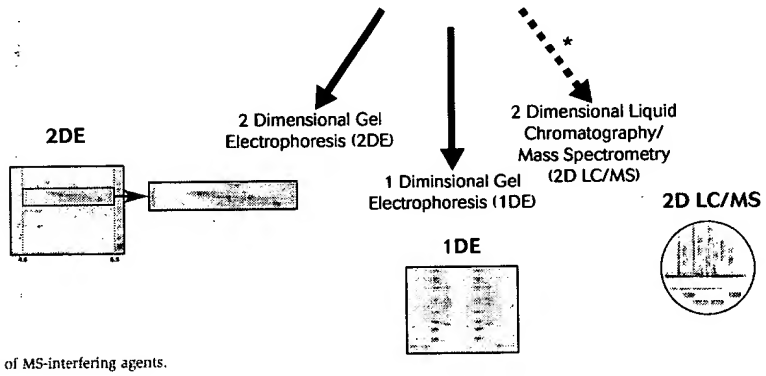
Solution phase IEF for proteomics analysis

The ZOOM® IEF Fractionator is designed to fractionate samples by isoelectric point prior to 2DE, 1DE, or 2D LC/MS analysis (Figure 1). This method provides a simple, convenient, and reliable means to reduce sample complexity and enrich low abundance proteins. The ZOOM® IEF Fractionator uses ready-to-use immobilized buffer disks to fractionate samples into five pI ranges, at a scale and cost accessible to any lab.

Figure 1 - ZOOM® IEF fractionation



* Requires removal of MS-interfering agents.

Biomarker discovery made easy

Successful biomarker discovery through protein profiling can be a challenge to researchers faced with the task of identifying low abundance proteins in a complex sample. The ZOOM® IEF Fractionator rapidly concentrates proteins into zones of isoelectric point so that higher loads of rare proteins are ready for further analysis. Even with powerful techniques, such as two-dimensional electrophoresis (2DE), one-dimensional electrophoresis (1DE), and 2D Liquid Chromatography/Mass Spectrometry (2D LC/MS), reducing the complexity of the sample is often necessary for optimal detection efficiency. The convenience of the ZOOM® IEF Fractionator makes it easy and fast to perform this initial fractionation at a price any lab can afford.

The ZOOM® IEF Fractionator (Figure 2) combines reproducibility with user-friendly design. You get all the capabilities you require in a convenient, accessible format:

- Solution phase isolectric focusing (IEF)
- Small volume capability (670 µl of sample/chamber)
- Easy set up and sample recovery
- Integrated buffer chambers
- Removable electrode assembly
- Built-in safety features

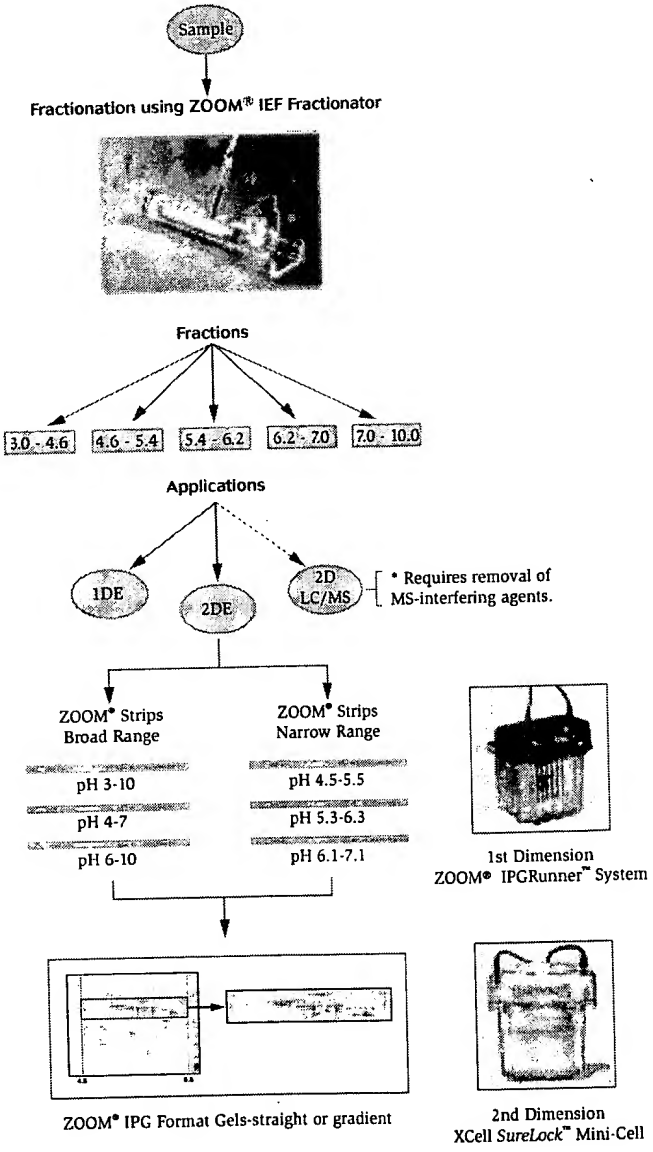
Advantages of ZOOM® IEF fractionation

Fractionation of proteins, especially highly complex samples like cell or tissue lysates, with the ZOOM® IEF Fractionator:

- Allows loading of increased amounts of proteins on IPG strips
- Results in high protein resolution and enhanced detection of low abundance proteins
- Increases sensitivity of detection, resulting in increased dynamic range of detection
- Reduces precipitation/aggregation artifacts of samples at high protein loads during 2DE

Figure 2 - ZOOM® IEF fractionation: application for 2DE

The flow path for fractionation of rat liver lysate using the ZOOM® IEF Fractionator. In addition, the flow path details the processing of fractionated sample by 2DE.



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ZOOM® Disks maximize reliability

The ZOOM® IEF Fractionator's unique immobilized buffer disks—ZOOM® Disks (Figures 3, 4, and 5)—are convenient to use and ensure consistent fractionation. ZOOM® Disks are provided at pH values designed to separate typical proteomes into fractions having similar numbers of proteins based on genome analysis. The pre-cast disks are gel-based and disposable, designed for single use to minimize any chance of cross contamination. Pre-marked with the pH of the separation matrix, they are easy to handle and load with no preparation necessary.

ZOOM® Disks of specific pH ranging from pH 3 to pH 10 are available, allowing the fractionation of your sample into five equal fractions. Simply place each disk between the sample chambers in the ZOOM® IEF Fractionator to allow separation in a specific pH range. For example, if you want to fractionate proteins between pH 4.6 and 5.4, connect two sample chambers separated by ZOOM® Disks of pH 4.6 and pH 5.4. Sample fractions from the ZOOM® IEF Fractionator can be analyzed further by focusing on three broad range or three narrow range (single pH gradient) ZOOM® Strips (*i.e.*, pH 4-7 or 4.5-5.5, respectively, for analyzing the 4.6-5.4 fraction mentioned above).

Figure 3 - ZOOM® Disks

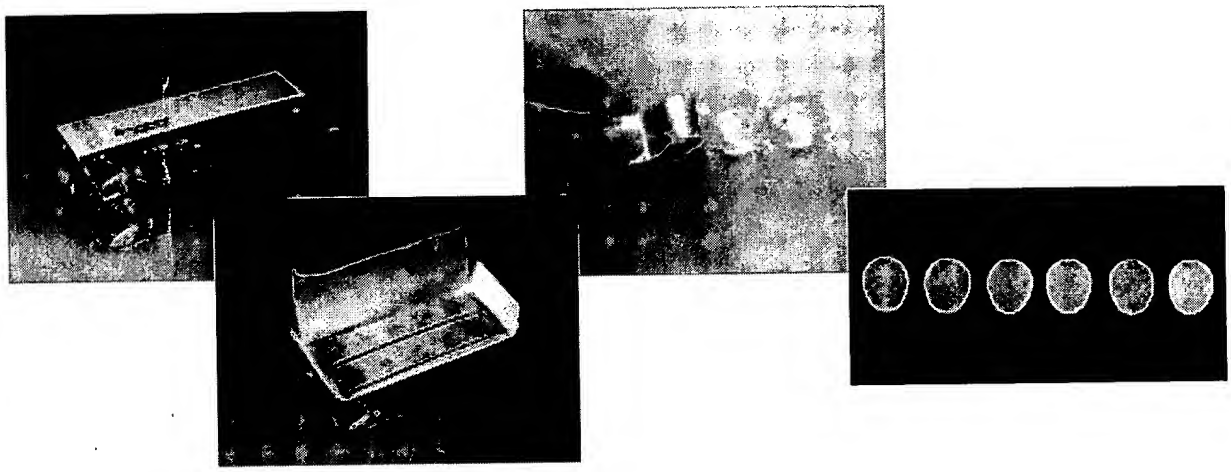


Figure 4 - ZOOM® IEF Fractionator components

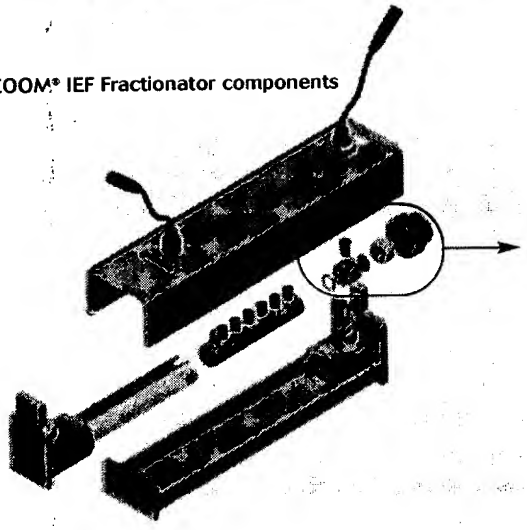
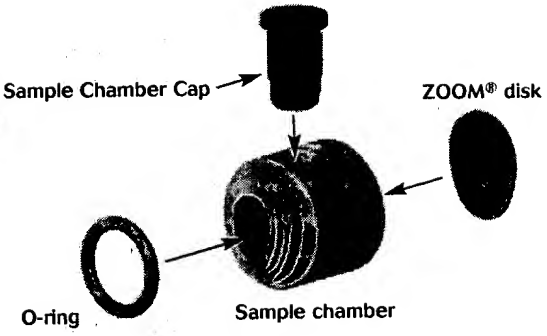


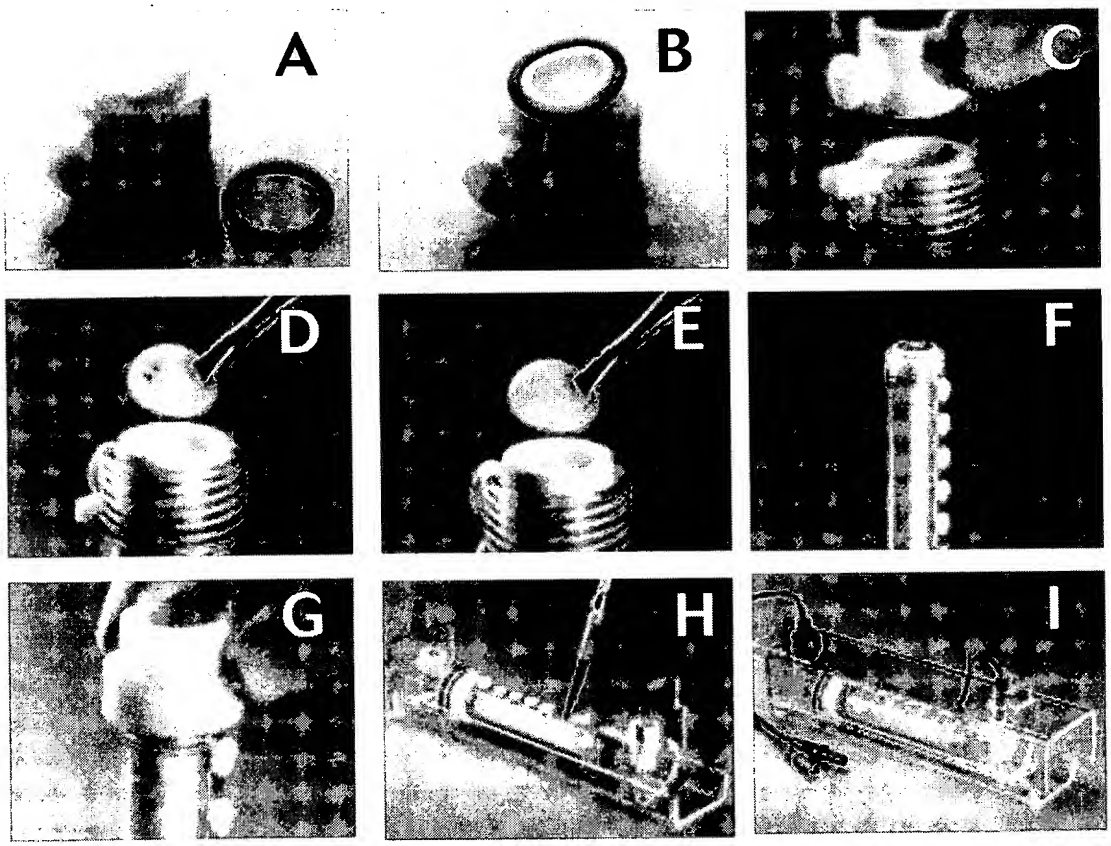
Figure 5 - Sample chamber assembly



Simple set up, easy run

The ZOOM® IEF Fractionator is designed for ease of use. First, set up the sample chambers (Figures 6 A through E) by inserting the pre-labeled ZOOM® Disks. Next, assemble the unit to form the buffer chambers and fill them with the appropriate buffers and samples (Figures 6 F through H). When you are ready to run, insert the lid (Figure 6I), and connect the electrodes to the power supply. Following a three-hour IEF run, the proteins are focused into five fractions. You'll have great spot resolution when the samples are processed further by 2DE, 1DE, or 2D LC/MS.

Figure 6 - ZOOM® IEF Fractionator sample chamber and unit set up



A. Insert Sample Chamber Cap into each chamber
B. Insert Sample Chamber O-ring in the front groove of each chamber
C. Insert anode end sealer into chamber assembly tube, then the first assembled sample chamber
D. Insert the appropriate ZOOM® Disk
E. Repeat steps to assemble the remaining sample chambers and disk
F. Complete process with the Cathode End Sealer
G. Screw in the Cathode End Screw Cap
H. Complete final assembly, add the samples and buffers, and insert the lid
I. Insert the lid and connect the electrodes to the power supply

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Clear, reproducible results

The ZOOM® IEF Fractionator provides the reliability you need for successful biomarker discovery in downstream applications. To demonstrate this, rat liver lysate (RLL) was fractionated using the ZOOM® IEF Fractionator, followed by analysis of the fractions using broad range (pH 3-10, 4-7, and 6-10) and narrow range (pH 4.5-5.5) ZOOM® Strips. Figure 7a shows that the ZOOM® IEF Fractionator System can efficiently separate a complex proteome, such as rat liver tissue, into five well defined fractions based on pH. The fractionation reduces the sample's complexity while increasing the concentration of the fractionated proteins. Figures 7b demonstrates the improved ability to detect low abundance proteins in the fractionated sample that was applied to the narrow range ZOOM® Strip compared to the complex, unfractionated rat liver lysate protein sample (Figure 7c).

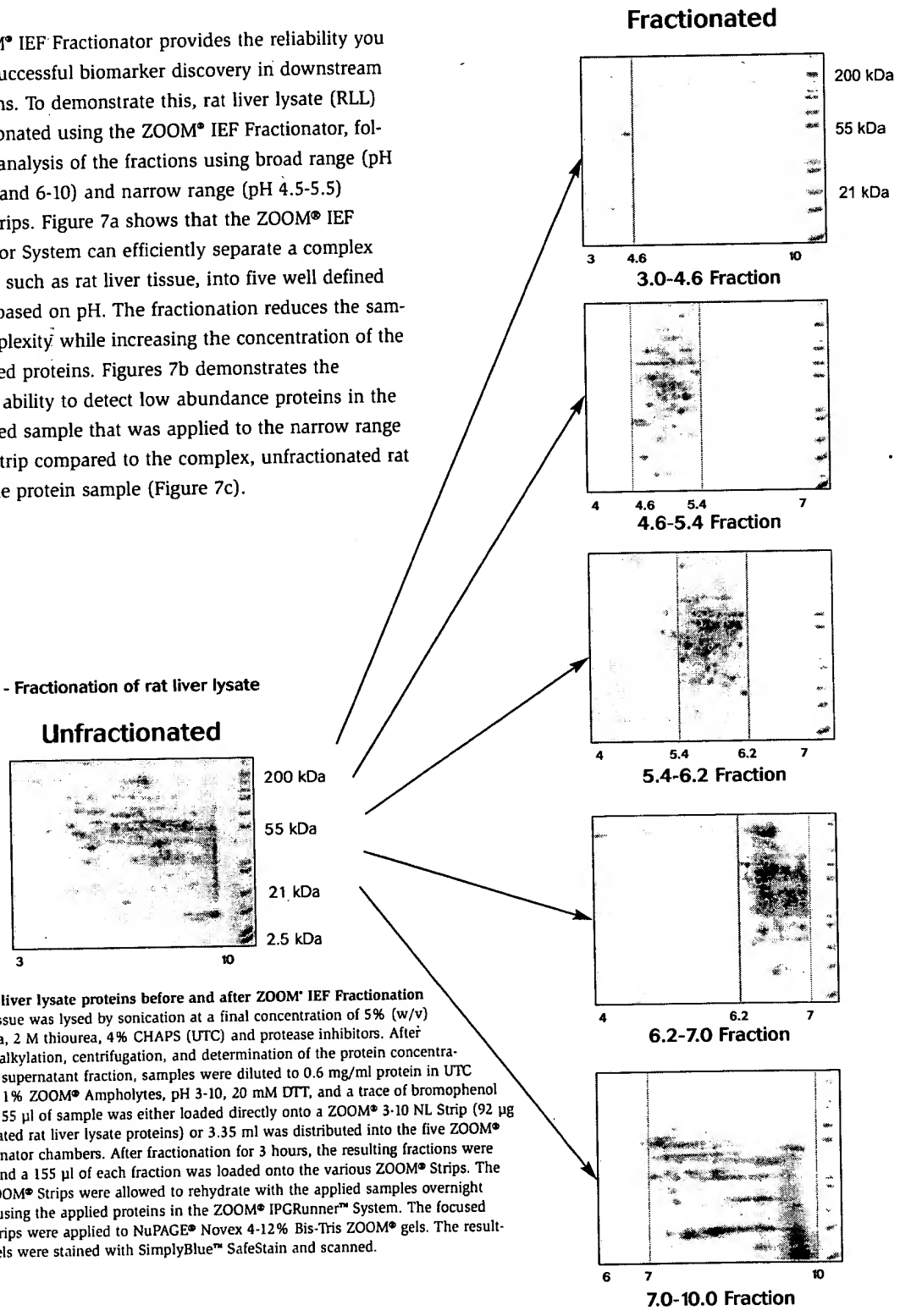
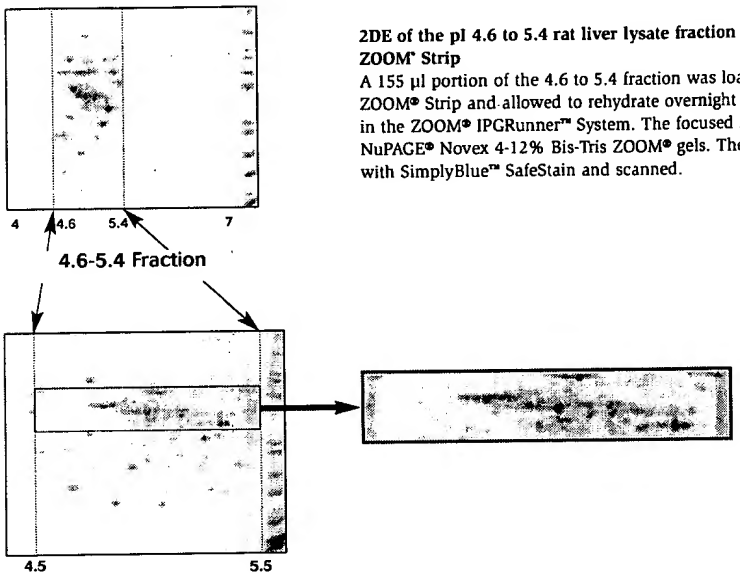


Figure 7a - Fractionation of rat liver lysate

2DE of rat liver lysate proteins before and after ZOOM® IEF Fractionation
Rat liver tissue was lysed by sonication at a final concentration of 5% (w/v) in 7 M urea, 2 M thiourea, 4% CHAPS (UTC) and protease inhibitors. After reduction, alkylation, centrifugation, and determination of the protein concentration of the supernatant fraction, samples were diluted to 0.6 mg/ml protein in UTC containing 1% ZOOM® Ampholytes, pH 3-10, 20 mM DTT, and a trace of bromophenol blue dye. 155 µl of sample was either loaded directly onto a ZOOM® 3-10 NL Strip (92 µg unfractionated rat liver lysate proteins) or 3.35 ml was distributed into the five ZOOM® IEF Fractionator chambers. After fractionation for 3 hours, the resulting fractions were collected and a 155 µl of each fraction was loaded onto the various ZOOM® Strips. The various ZOOM® Strips were allowed to rehydrate with the applied samples overnight before focusing the applied proteins in the ZOOM® IPGRunner™ System. The focused ZOOM® Strips were applied to NuPAGE® Novex 4-12% Bis-Tris ZOOM® gels. The resulting 2DE gels were stained with SimplyBlue™ SafeStain and scanned.

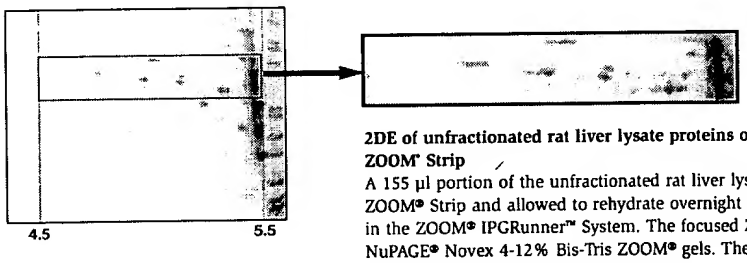
Clear, reproducible results, *continued*

Figure 7b - Fractionated rat liver lysate proteins



2DE of the pI 4.6 to 5.4 rat liver lysate fraction on a pH 4.5-5.5 narrow range ZOOM® Strip
A 155 µl portion of the 4.6 to 5.4 fraction was loaded on a pH 4.5-5.5 narrow range ZOOM® Strip and allowed to rehydrate overnight before focusing the applied proteins in the ZOOM® IPGRunner™ System. The focused ZOOM® Strips were applied to NuPAGE® Novex 4-12% Bis-Tris ZOOM® gels. The resulting 2DE gels were stained with SimplyBlue™ SafeStain and scanned.

Figure 7c - Unfractionated rat liver lysate proteins



2DE of unfractionated rat liver lysate proteins on a pH 4.5 to 5.5 narrow range ZOOM® Strip
A 155 µl portion of the unfractionated rat liver lysate was loaded on a 4.5-5.5 ZOOM® Strip and allowed to rehydrate overnight before focusing the applied proteins in the ZOOM® IPGRunner™ System. The focused ZOOM® Strips were applied to NuPAGE® Novex 4-12% Bis-Tris ZOOM® gels. The resulting 2DE gels were stained with SimplyBlue™ SafeStain and scanned.

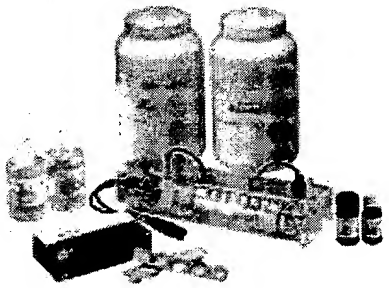
ZOOM® Strips and the ZOOM® IPGRunner™ System: more innovative tools for benchtop proteomics

Three narrow range (1.0 pH unit) ZOOM® Strips from Invitrogen are fully compatible with three corresponding ZOOM® IEF Fractions. You can use narrow or broad range ZOOM® Strips on the ZOOM® IPGRunner™ System. The ZOOM® IPGRunner™ System provides a quick and convenient way to perform IEF of proteins using IPG strips for 2DE. For more details on the ZOOM® IPGRunner™ System, visit **www.invitrogen.com/zoom**.

Take the first step to successful biomarker discovery

Increase the resolution and detection of your protein samples with the simplicity, speed, and savings that the ZOOM® IEF Fractionator can offer. Order yours today.

Product	Quantity	Cat. no.
ZOOM® Fractionator Combo Kit	1 kit*	ZF10001
ZOOM® IEF Fractionator	1 ea	ZF10002
ZOOM® Disk pH 3.0	10 disks/pack	ZD10030
ZOOM® Disk pH 4.6	10 disks/pack	ZD10046
ZOOM® Disk pH 5.4	10 disks/pack	ZD10054
ZOOM® Disk pH 6.2	10 disks/pack	ZD10062
ZOOM® Disk pH 7.0	10 disks/pack	ZD10070
ZOOM® Disk pH 10.0	10 disks/pack	ZD10010
ZOOM® Urea	1 kg	ZU10001
ZOOM® Thiourea	1 kg	ZT10002
ZOOM® CHAPS	0.5 g	ZC10003
ZOOM® Carrier Ampholytes pH 3-10	10 ml	ZM0021
Novex® IEF Anode Buffer (50X)	100 ml	LC5300
Novex® IEF Cathode Buffer (10X)	125 ml	LC5310



* Includes all items in the quantity listed: ZOOM® IEF Fractionator; one pack ZOOM® Disks of each pH; urea; thiourea; CHAPS; carrier ampholytes pH 3-10; anode and cathode buffers.

References:

1. Zuo, X. and Speicher, D.W. (2000) *Anal. Biochem.* **284:** 266-278.
2. Zuo, *et al.* (2001) *Electrophoresis* **22:** 1603-1615.
3. Zuo and Speicher (2002) *Proteomics* **2:** 58-68.
4. Zuo, X., Hembach, P., Echan, L., and Speicher, D.W. (2002) *Journal of Chromatgraphy B* **782:** 253-265.
5. Ali-Khan, N., Zuo, X., and Speicher, D.W. (2002) *Current Protocols in Protein Science* **22.1:** 1-19.
6. Zuo, X. and Speicher D.W. (2002) *Methods in Molecular Biology* (Humana Press, P. Cutler, ed.) In press.

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1: Biochem Biophys Res Commun. 1998 Apr 28;245(3):764-73.

Related Articles, Links

ELSEVIER FULL-TEXT ARTICLE

Bactericidal domain of lactoferrin: detection, quantitation, and characterization of lactoferricin in serum by SELDI affinity mass spectrometry.

Kuwata H, Yip TT, Yip CL, Tomita M, Hutchens TW.

Department of Food Science and Technology, University of California, Davis 95616, USA. Hidi@msn.com

Lactoferricin is a bioactive peptide fragment (3196 Da) derived from lactoferrin (80 kDa) that contains the bactericidal domain and the lymphocyte receptor-binding domain of lactoferrin. Although lactoferricin has been produced from lactoferrin by proteolytic digestion in vitro, its natural occurrence and distribution in vivo are still not clear, in part because of the absence of a suitable detection means. Surface-enhanced laser desorption/ionization (SELDI) was used to detect and characterize lactoferricin by affinity mass spectrometry. Human, porcine, and bovine lactoferricin in unfractionated serum samples were found to bind specifically to ligands presenting a terminal n-butyl group. SELDI was used to detect and quantify each species of lactoferricin in a manner that was independent of the presence of intact lactoferrin, partially degraded lactoferrin, and lactoferrin peptides containing the lactoferricin peptide sequence. The limit of detection of bovine lactofericin in serum was as low as 200 pg/ml. The FKCRRWQWR-homoserine/-homoserine lactone moiety of bovine lactoferricin, which includes the complete antimicrobial center (i.e., RRWQWR), was shown to be responsible for interaction with the n-butyl group. The SELDI procedure defined here is the only molecular recognition tool known to date that is capable of distinguishing the multi-functional lactoferricin domain located within structurally related but distinct forms of lactoferrin and its metabolic fragments. Enabling the direct quantitation of lactoferricin produced in vivo opens new opportunities to evaluate lactoferrin function.

PMID: 9588189 [PubMed - indexed for MEDLINE]

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cerebrospinal fluid
n. Abbr. **CSF**

The serumlike fluid that circulates through the ventricles of the brain, the cavity of the spinal cord, and the subarachnoid space, functioning in shock absorption.

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reference 5

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Pseudotumor cerebri and its medical treatment.

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Pseudotumor cerebri is an idiopathic disorder characterized by papilledema and elevated intracranial pressure without a mass lesion. Most patients are female and young and are either overweight or have a history of recent weight gain. Other disease states, such as systemic lupus erythematosus, and drugs, such as tetracycline, have also been associated with the development of pseudotumor cerebri. The mechanism is unclear, but is likely related to decreased cerebrospinal fluid (CSF) resorption. Almost all patients have headache, but the greatest morbidity of the disorder is visual loss related to optic disc swelling. Common radiographic findings in pseudotumor cerebri include an empty sella, dilation of the optic nerve sheaths and elevation of the optic disc. The CSF, aside from elevated opening pressure, is normal without evidence of infection or inflammation. Treatment of patients with no or mild to moderate visual loss is primarily medical, with acetazolamide as the first-line agent. Acetazolamide decreases CSF production. Furosemide and corticosteroids are secondary choices. Optic nerve surgery is reserved for patients with severe visual loss or progression in visual deficits despite medical management.

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